

Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)

Lip, Gregory Y.h.; Hammerstingl, Christoph; Marin, Francisco; Cappato, Riccardo; Meng, Isabelle Ling; Kirsch, Bodo; Morandi, Eolo; Van Eickels, Martin; Cohen, Ariel

DOI:

[10.1016/j.ahj.2014.12.020](https://doi.org/10.1016/j.ahj.2014.12.020)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Lip, GYH, Hammerstingl, C, Marin, F, Cappato, R, Meng, IL, Kirsch, B, Morandi, E, Van Eickels, M & Cohen, A 2015, 'Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)', *American Heart Journal*, vol. 169, no. 4, pp. 464–471.e2. <https://doi.org/10.1016/j.ahj.2014.12.020>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 04. May. 2023

Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)

Gregory Y. H. Lip, MD,^a Christoph Hammerstingl, MD,^b Francisco Marin, MD,^c Riccardo Cappato, MD,^d Isabelle Ling Meng, MD, PhD,^e Bodo Kirsch, MSc,^f Eolo Morandi, MD,^g Martin van Eickels, MD,^e and Ariel Cohen, MD, PhD^h *Birmingham, United Kingdom; Bonn, Berlin, Germany; Murcia, Spain; Milan, Italy; São Paulo, Brazil; and Paris, France*

There are still many unresolved issues concerning patient outcomes and prognostic factors in patients with atrial fibrillation (AF) and left atrial/left atrial appendage (LA/LAA) thrombi. Rivaroxaban (Xarelto®), a potent and highly selective oral, direct factor Xa inhibitor, is a new therapeutic option in this setting. The planned study program will consist of a prospective interventional study (X-TRA) and a retrospective observational registry (CLOT-AF).

The primary objective of the X-TRA study is to explore the efficacy of rivaroxaban in the treatment of LA/LAA thrombi in patients with nonvalvular AF or atrial flutter, scheduled to undergo cardioversion or AF ablation, in whom an LA/LAA thrombus has been found on transesophageal echocardiography (TEE) before the procedure. The primary end point is the complete LA/LAA thrombus resolution rate at 6 weeks of end of treatment confirmed by TEE. The secondary objectives are to describe categories of thrombus outcome in patients (resolved, reduced, unchanged, larger, or new) confirmed on TEE at the end of treatment (after 6 weeks of treatment), incidence of the composite of stroke and noncentral nervous system systemic embolism at the end of treatment and during follow-up, and incidence of all bleeding at the end of treatment and during follow-up.

The objective of the CLOT-AF registry is to provide retrospective thrombus-related patient outcome data after standard-of-care anticoagulant treatment in patients with nonvalvular AF or atrial flutter, who have TEE-documented LA/LAA thrombi. The data will be used as a reference for the prospective X-TRA study.

In conclusion, X-TRA and CLOT-AF will provide some answers to the many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LAA thrombi. Results from this study program would provide the first prospective interventional study (X-TRA) and a large international retrospective observational registry (CLOT-AF) on the prevalence and natural history of LA/LAA thrombi. Unique data on clot resolution with rivaroxaban in a prospective cohort would be obtained in X-TRA. (Am Heart J 2015;169:464-471.e2.)

Atrial fibrillation (AF) predisposes to the development of atrial thrombi, most commonly in the left atrial (LA) appendage (LAA), which is the dominant source of embolism

(>90%) in nonvalvular AF.¹ Poor-quality anticoagulation, especially where time in therapeutic range (international normalized ratio [INR] 2.0-3.0) is poor or before

From the ^aUniversity of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom, ^bDepartment of Medicine II, Heart Center Bonn, University Hospital, Bonn, Germany, ^cDepartment of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, Murcia, Spain, ^dArrhythmia and Electrophysiology Center, University of Milan, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy, ^eGlobal Medical Affairs, Bayer HealthCare, Berlin, Germany, ^fGlobal Research and Development Statistics, Bayer HealthCare, Berlin, Germany, ^gTherapeutic Cardiovascular and Coagulation, Global Development, Bayer HealthCare, São Paulo, Brazil, and ^hCardiology Department, Assistance Publique-Hôpitaux de Paris and Université Pierre-et-Marie-Curie, Saint-Antoine University and Medical School, Paris, France.

Randomized controlled trial nos.: NCT01839357 (X-TRA study) and NCT01928979 (CLOT-AF registry).

Submitted July 31, 2014; accepted December 4, 2014.

Reprint requests: Professor G.Y.H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom. E-mail: g.y.h.lip@bham.ac.uk

0002-8703

© 2015 The Authors. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.ahj.2014.12.020>

establishment of effective oral anticoagulation, is associated with an increase in the risks of stroke and thromboembolism.^{2,3} Unresolved thrombi in the LAA (identified in 10% of patients with AF and at high risk of thromboembolism) may result in an increased subsequent risk of thromboembolic events.^{4,6} For example, during the initial control phase of the Ludwigshafen Observational Cardioversion Study, in the conventional approach (using transesophageal echocardiography), LA/LAA thrombus was found in the left atrium in 7.7% of cases, and 3 thromboembolic events occurred in the first 4 weeks after cardioversion (CV) (0.8%), a rate similar to that observed in the prospective TEE group.⁷

Transesophageal echocardiography is well established as the criterion standard for evaluation of the LA/LAA for the presence of thrombi.⁸⁻¹¹ If an LA/LAA thrombus is detected during TEE evaluation, current AF guidelines include treatment with vitamin K antagonist (VKA) therapy for 3 weeks, with an INR ranging from 2.0 to 3.0.¹² A follow-up TEE assessment at 3 weeks is recommended to ensure thrombus resolution.¹²

Cardioversion is one of the therapeutic options used to restore sinus rhythm; however, the procedure may result in dislodgment of LA thrombi or lead to new thrombus formation owing to atrial stunning after CV and is associated with an increased risk of stroke.^{4,13,14} A treatment option is to perform immediate CV in patients with symptomatic AF after exclusion of LA thrombi with TEE under effective anticoagulation with short-acting anticoagulants. After a median of 4 weeks on warfarin therapy, the resolution rates of the thrombi on TEE were reported to be approximately 50% to 90%.^{4,7,9,14-16} The wide range of resolution rates was caused by different populations (eg, those that did or did not include valvular AF; first diagnosed or persistent AF), different anticoagulation, and/or imaging strategies evaluated in relatively small observational studies.

Owing to the low incidence of LA/LAA thrombi in patients with AF, data are limited. In ROCKET AF, 321 patients underwent a total of 460 CV or AF ablation procedures.¹⁷ Only small retrospective or prospective observational studies have been published (online [Appendix Supplementary Table D](#)). In a post hoc analysis of the ARISTOTLE trial, no LA thrombi were found in 171 patients who underwent TEE.¹⁸

Data for the non-VKA oral anticoagulants (NOACs) (previously called new or novel OACs) are presently limited¹⁹ with regard to the treatment and outcome of patients with AF and LA/LAA thrombus, and these data largely comprise case reports. Non-VKA oral anticoagulants may offer several advantages in their relative efficacy, safety, and convenience as well as fast onset of therapeutic anticoagulation, when LA/LAA thrombus is detected.^{20,21}

Several case reports indicate favorable outcomes in thrombus patients treated with NOACs, in which VKAs

failed to resolve LA thrombi. In 1 case, LAA thrombus was resolved after 7 weeks' treatment with dabigatran. This patient failed to achieve INR >2 after 2 weeks of dose-adjusted VKA therapy before switching to dabigatran.²² Results of a preliminary publication have shown that, among 487 patients undergoing TEE before electrical CV or before AF ablation, when stratified by type of anticoagulation, dabigatran use was associated with a 4.6-times higher likelihood of LAA thrombi compared with warfarin (odds ratio 4.6 [1.6-21] $P = .003$) and 6.2-times higher likelihood compared with rivaroxaban (odds ratio 6.2 [1.9-31] $P = .002$).²³ After 4 weeks' treatment with rivaroxaban 15 mg once daily in a 64-year-old man, TEE showed a decrease in thrombus size; 6 weeks' treatment resulted in complete resolution of the LAA thrombus.²⁴ In addition, Takasugi et al²⁵ described a set of 3 cases in which patients with nonvalvular AF-related stroke had resolution of LAA thrombi within 8 to 33 days of rivaroxaban treatment. Apixaban was also shown to completely resolve LA thrombus in a 72-year-old man, after 16 days of treatment.²⁶ In an 86-year-old man, 11 weeks of apixaban therapy led to almost complete resolution of LA thrombus.²⁷ Studies examining TEE detection and thrombus resolution are described in online [Appendix Supplementary Table I](#).

It is possible that the potential mechanism of action of NOACs allows for relatively higher thrombus resolution rates compared with the VKAs.²⁸ The current published case reports encourage further investigations in this field.

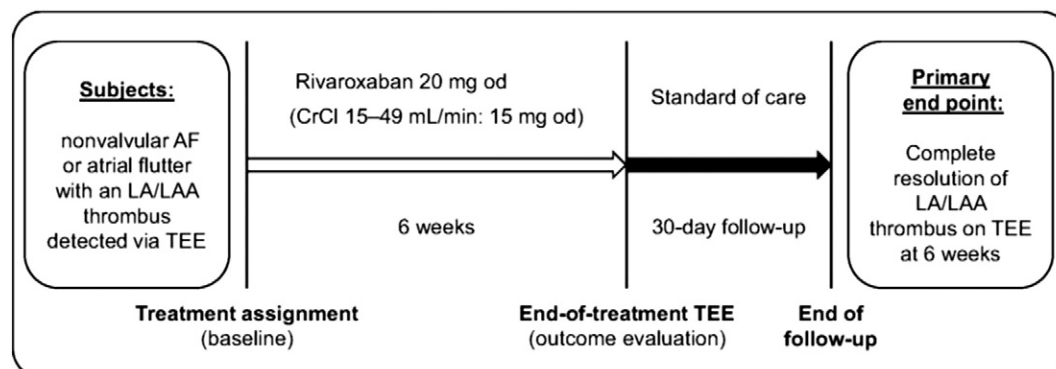
Rationale

There are still many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LA/LAA thrombi. Rivaroxaban, a potent and highly selective, oral, direct factor Xa inhibitor, is a new therapeutic option in this setting.²⁹ The planned study program will consist of a prospective interventional study (X-TRA; Xarelto – ThRombus Accelerated resolution) and a retrospective observational registry (CLOT-AF). The CLOT-AF registry was developed in light of the limited data on the prevalence and natural history of LA/LAA thrombi, and we wished to acquire center-specific data from the study sites undertaking X-TRA.

Study objectives and end points

X-TRA

The primary objective of this study (ClinicalTrials.gov identifier NCT01839357) is to explore the efficacy of rivaroxaban in the treatment of LA/LAA thrombi in patients with nonvalvular AF or atrial flutter, scheduled to undergo CV or AF ablation, in whom an LA/LAA thrombus has been found on TEE before procedure. The primary end point is the complete LA/LAA thrombus resolution rate at 6 weeks

Figure 1

X-TRA study design. *CrCl*, creatinine clearance; *od*, once daily.

of end of treatment confirmed by TEE. The term *non-valvular AF* is used to imply that AF is not related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.²¹

The secondary objectives of the study are to describe categories of thrombus outcome in patients (resolved, reduced, unchanged, larger, or new) confirmed on TEE at the end of treatment (after 6 weeks of treatment), incidence of the composite of stroke and noncentral nervous system systemic embolism at the end of treatment and during follow-up, and incidence of all bleeding (major and nonmajor) events at the end of treatment and during follow-up.

The exploratory objectives of the study in the VKA/NOAC naïve/untreated subgroup are to evaluate biomarkers of prothrombotic status (plasma prothrombin fragment 1 + 2 and thrombin-antithrombin complexes), inflammatory response (high-sensitivity interleukin 6 [IL-6]; high-sensitivity C-reactive protein), thrombogenesis (D-dimers), fibrinolysis (plasminogen activator inhibitor type 1 [PAI-1] antigen), and endothelial damage/dysfunction (von Willebrand factor [vWF]).

CLOT-AF

The objective of this registry (ClinicalTrials.gov identifier NCT01928979) is to provide retrospective thrombus-related patient outcome data after standard-of-care anticoagulant treatment in patients with nonvalvular AF or atrial flutter, who have TEE-documented LA/LAA thrombi. The data will be used as a reference for the prospective X-TRA study.

The primary outcome of interest is thrombus resolution rate confirmed on TEE after 3 to 12 weeks of anticoagulant treatment based on the routine practice of the centers. Secondary end points are stroke or noncentral nervous system systemic thromboembolism rate and all bleeding (major, nonmajor, and unknown severity) rates.

External data evaluation bodies

X-TRA

A steering committee will be involved periodically in the planning, review, oversight of design, conduct, and study progress. The study outcome committee (SOC) will apply the protocol definitions (to be provided in the SOC manual) and will centrally adjudicate TEE results in a blinded fashion regarding pretreatment or posttreatment, but will not otherwise be involved in the study. Assessment of the SOC is the basis for the analysis of the efficacy end point.

CLOT-AF

In a subset of patients ($\geq 20\%$ of sites), source data verification will be conducted. The purpose is to review documented data for completeness and plausibility, adherence to study protocol, and verification with source documents. Depending on the local, legal, and ethical regulations as well as data protection laws, the reviewer will compare data in the case report form with data in the source. Transesophageal echocardiography data in CLOT-AF will not be centrally adjudicated.

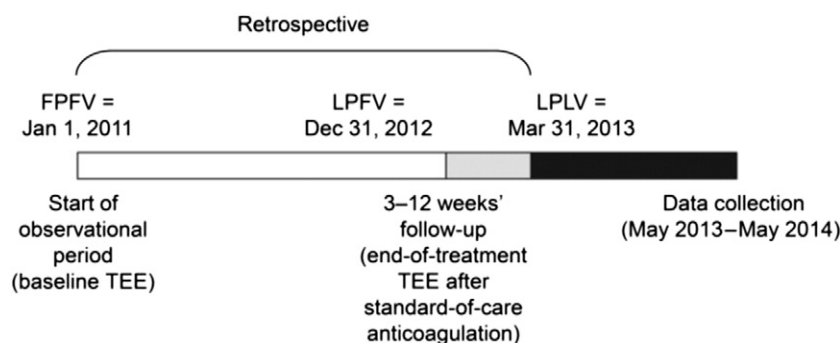
Study design

X-TRA

The X-TRA study is a prospective, single-arm, open-label, multicenter study. Owing to the expected low incidence of LA/LAA thrombi in patients with AF, the proposed study will be explorative in nature but will be the first prospective interventional study with a NOAC in this setting.

The study will be designed as described in Figure 1. At the end of the treatment period, TEE will be repeated and centrally adjudicated by the SOC. An additional TEE should be encouraged at the posttreatment follow-up visit for patients with residual thrombi.

Figure 2



Overview of CLOT-AF registry. FPFV, first patient, first visit; LPFV, last patient, first visit; LPLV, last patient, last visit.

CLOT-AF

CLOT-AF, a retrospective registry independent from the prospective interventional study, is planned in parallel to collect baseline data and outcome information from patients with nonvalvular AF or atrial flutter who received VKA treatment based on standard of care and have LA/LAA thrombus confirmed on TEE. This retrospective registry will be set up at the same study sites participating in the X-TRA study to collect thrombus outcome data during 2011 to 2012 as a historical baseline of standard of care.

Retrospective patient data were collected from May 2013 to May 2014. The observation of each patient covers the period from the diagnosis of an LA/LAA thrombus until the end-of-treatment TEE after the 3- to 12-week standard-of-care anticoagulation therapy (Figure 2). If no end-of-treatment TEE has been performed during 3 to 12 weeks of anticoagulant therapy, the observational period will end at 12 weeks after diagnosis, at the latest. If >1 TEE was performed during treatment, the thrombus outcome will be collected from the last TEE performed within 12 weeks of treatment start.

Eligible patients during the period from January 1, 2011 to December 31, 2012 are to be identified via screening and review of medical records, for inclusion in registry. This retrospective screening and review will occur between May 2, 2013 and May 2, 2014. The observation of each patient will cover the period from diagnosis of an LA/LAA thrombus until the end-of-treatment TEE after the 3- to 12-week standard-of-care anticoagulation therapy.

Ethics approval

For both X-TRA and CLOT-AF, documented approval from the appropriate independent ethics committees/institutional review boards will be obtained for all participating centers before the start of the study according to good clinical practice and local laws, regulations, and organizations.

Patient population X-TRA study

Men or women aged ≥ 18 years with hemodynamically stable nonvalvular AF or atrial flutter in whom LA/LAA thrombus has been documented at baseline by TEE up to 72 hours before the start of study drug treatment are eligible for inclusion. Eligible patients must be VKA/NOAC naive or untreated within 1 month before signing the informed consent form (treatment of up to 72 hours with VKA, heparin, or a low molecular weight heparin is allowed before the start of study drug treatment) or VKA pretreated but under ineffective INR levels (<2.0 documented with ≥ 2 consecutive measurements that are ≥ 24 hours apart) within the last 6 weeks.

Patients who meet any of the following cardiac-related criteria will be excluded: previous intracardiac thrombus, free-floating ball thrombus, intracardiac tumor (eg, known presence of atrial myxoma), known left ventricular or aortic thrombus, or active endocarditis. Patients with the following will be also excluded: calculated creatinine clearance <15 mL/min at the screening visit, hepatic disease that is associated with coagulopathy leading to a clinically relevant bleeding risk, or any severe condition that would limit life expectancy to <3 months (eg, advanced malignancy). Complete inclusion and exclusion criteria are described in online [Appendix Supplementary Table II](#).

CLOT-AF

Men or women aged ≥ 18 years with hemodynamically stable nonvalvular AF or atrial flutter in whom LA/LAA thrombus has been documented at baseline by TEE are eligible for inclusion.

Patients who meet any of the following cardiac-related criteria will be excluded: valvular AF (European Society of Cardiology 2012 definition),²¹ a history of cardiac thrombus confirmed on TEE, intracardiac tumors (eg, known presence of atrial myxoma), or active endocarditis.

Study drug

X-TRA study

Patients will be treated with 6 weeks of rivaroxaban 20 mg once daily, with a dose reduction to 15 mg once daily for patients with moderate-to-severe renal impairment (ie, creatinine clearance of 15–49 mL/min; inclusive) at screening.

CLOT-AF registry

Owing to the retrospective, observational nature of the CLOT-AF registry, the choice of anticoagulant was left to the discretion of the treating physician.

Transesophageal echocardiography

Transesophageal echocardiography will be performed according to standard procedures at screening and at the end of treatment. If a residual or new thrombus is confirmed on the end-of-treatment TEE, performance of an additional TEE should be encouraged at the end of the follow-up period. Transesophageal echocardiography data obtained before the screening visit will be collected on DVD or in electronic format for review by the SOC as baseline. In the X-TRA study, TEE images will be recorded by the investigator for the SOC to adjudicate the primary end point and confirm the presence of a thrombus. The results of the third TEE (if performed) will be reported in the electronic case report form by the investigators.

Data to be collected include number, size, location, mobility of thrombus/thrombi for primary outcome, and evolution of the LA/LAA thrombus, for example, resolved, reduced in size, stable (unchanged size), or worsened (increased in size or new thrombus). All examinations should be recorded for adjudication and to differentiate thrombus from severe (“sludge”) left atrial spontaneous echo contrast.

Biomarkers

The effect of rivaroxaban will be explored in the study population with respect to coagulation, inflammatory response, fibrinolysis, and endothelial damage/dysfunction. A blood sample will be obtained only in the VKA/NOAC naive/untreated subgroup at screening and at the end of treatment (or at the time of early discontinuation of study drug treatment if blood sampling can occur within 24 hours after the last dose of study drug).

In several studies, coagulation biomarkers, such as fibrin D-dimers, were elevated in patients with AF and those with LA thrombi.^{30–33} A sufficient anticoagulant effect is mirrored by a significant decrease of coagulation biomarkers.^{34,35} Left atrial thrombi presence is associated with elevated plasma C-reactive protein levels,³⁶ and the proinflammatory cytokine IL-6 is suspected to have a role in thrombogenesis.^{37,38} It has been shown that plasma IL-6 levels are related to markers of prothrombotic state of patients with AF.³⁰ Plasminogen activator inhibitor type 1

inhibits endogenous fibrinolysis, and plasma PAI-1 levels are increased in patients with AF.³⁹ Expression of PAI-1 has been shown to be upregulated in the left atrium in AF and could have a role in thrombogenesis.⁴⁰ Further investigations revealed that PAI-1 decreases significantly upon anticoagulation therapy.⁴¹

Plasma vWF plays an important role in platelet adhesion to the subendothelium. Furthermore, vWF regulates thrombus formation by interacting with glycoprotein complexes.⁴² It is an established biomarker of endothelial damage and/or dysfunction. It was found that high vWF was associated with future adverse cardiovascular events and mortality in patients with permanent AF.⁴³ Patients with AF and LAA thrombus had higher vWF antigen activity compared with those without LAA thrombus.⁴⁴ Several other studies have emphasized the use of plasma vWF to stratify risk and predict outcome in AF.^{45,46}

Statistical analysis plan

Statistical analyses will be exploratory and descriptive and are not powered to test any specific hypothesis. The estimated sample size is based on the expected presence of an LA/LAA thrombus detected on TEE in the study sites participating in the enrollment period. The reported incidence of LA/LAA thrombus is varied and low, in the region of 5% to 15%.¹² Online [Appendix Supplementary Table I](#) describes the incidence of LA/LAA thrombus in published literature, with most studies identifying LA/LAA thrombi in <60 patients. One study identified LAA thrombi in 151 of 9,058 patients. Therefore, it is determined that the target enrollment for the X-TRA study is 60 patients. With 60 evaluable subjects the width of the 95% CI for the primary variable is expected to be 0.26 (26 percentage points) or less depending on the observed resolution rate.

The primary outcome measure is the complete resolution of LA/LAA thrombus. This will be evaluated on a per-patient basis. The definition of complete thrombus resolution for a patient refers to being completely thrombus free in the left atrium. This will be based on the end-of-treatment TEE as determined by independent adjudication by the SOC. The primary analysis will evaluate this outcome on the modified intent-to-treat population (patients with LA thrombus at baseline who have an evaluable end-of-treatment TEE after 6 weeks of treatment). Sensitivity analysis of the primary outcome will be based on the intent-to-treat population, in which patients without an evaluable TEE will be considered to still have a thrombus in this summary. Exact (Clopper-Pearson) 95% CIs for the probability of a present thrombus in the LA/LAA will be calculated.

The secondary outcome measure will evaluate the outcome of thrombi after 6 weeks' treatment relative to patients observed at study entry. For this evaluation, patients will be categorized according to the worst change in thrombus noted on the end-of-treatment TEE compared with the baseline TEE. Individual thrombi will be evaluated

(in increasing order of severity) as resolved, reduced, unchanged, or enlarged since baseline or new as compared with baseline, and patients will be categorized according to the most severe category into which any thrombus falls. Rates will be provided for each category, and 95% CIs for the probability of belonging to the combined categories of resolved/reduced and unchanged/enlarged/new will be calculated.

Discussion

Non-VKA oral anticoagulants are increasingly being used for the prevention and treatment of thrombi formation owing to the inherent limitations of VKAs, such as difficulty in maintaining patients within a narrow therapeutic range and the need for regular INR measurements.^{47,48} The NOACs work by directly inhibiting either thrombin or factor Xa, reducing thrombus formation. The differences in the mechanisms of action may be a factor in resolution of LA/LAA thrombi in patients with AF. Direct thrombin inhibitors such as dabigatran prevent thrombin from activating fibrinogen into fibrin. Conversely, rivaroxaban, apixaban, and edoxaban target factor Xa, preventing it from activating prothrombin to thrombin. Factor Xa is considered to be a particularly appropriate target for thrombus inhibition because of its convergent position between the intrinsic and extrinsic coagulation pathways,⁴⁹ with 1 molecule of factor Xa also responsible for the generation of >1000 thrombin molecules.⁵⁰ In addition, direct thrombin inhibitors may downregulate protein C to a greater extent than factor Xa inhibitors⁵¹ and consequently downregulate protein C-mediated anticoagulant pathways.⁵²

X-TRA and CLOT-AF will provide some answers to the many unresolved issues concerning patient outcomes and prognostic factors in patients with AF and LAA thrombi. Results from this study program would provide the first data on the prevalence and natural history of LA/LAA thrombi. In addition, unique data on clot resolution with rivaroxaban in a prospective cohort would be obtained in X-TRA.

Conflicts of interest

G.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Böhringer Ingelheim, and has been on the speakers bureau for Bayer, BMS/Pfizer, Böhringer Ingelheim, Daiichi-Sankyo, Medtronic, and Sanofi Aventis. C.H. receives research grants from Sanofi-Aventis and speaker honoraria from Bayer HealthCare, Böhringer Ingelheim, and Pfizer. F.M. has received funding for research, consultancy, and lecturing from Abbott, Boston Scientific, Bayer, AstraZeneca, Daiichi-Sankyo, BMS/Pfizer, and Böhringer Ingelheim. R.C. has received consultancy fees or research funding from Boston Scientific, Medtronic, St Jude, Biosense Webster, Böhringer Ingelheim, Bayer

HealthCare, Abbott, ELA Sorin, Pfizer, and BARD, and has equity and intellectual property rights in Cameron. I.L.M., B.K., E.M., and M.v.E. are employees of Bayer HealthCare. A. C. has received a research grant for research nurses (RESICARD) and consultant and lecture fees from AstraZeneca, Bayer Pharma, Böhringer-Ingelheim, BMS, Daiichi Sankyo, GlaxoSmithKline, and Sanofi-Aventis.

Acknowledgements and disclosures

We thank the SOC, chaired by Professor Dr Martin Prins, for their work in a challenging task. We also thank the following Bayer employees: CLOT-AF registry project manager, Dr Monika Brunn; the CLOT-AF epidemiology expert, Dr Kiliana Suzart-Woischnik; and the X-TRA study medical expert, Dr Eliana Samano for their significant contribution to the study design. The authors would also like to acknowledge Vicky Hinstridge, who provided editorial assistance with funding from Bayer HealthCare Pharmaceuticals and Janssen Scientific Affairs, LLC. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the paper, and its final contents.

References

1. Al Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999;82:547-54.
2. Azoulay L, Dell'aniello S, Simon TA, et al. Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes. *Eur Heart J* 2014;35:1881-7.
3. Gallego P, Roldan V, Marin F, et al. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. *Thromb Haemost* 2013;110:1189-98.
4. Corrado G, Tadeo G, Beretta S, et al. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* 1999;115:140-3.
5. Nagarankanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;123:131-6.
6. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Ann Intern Med* 1998;128:639-47.
7. Seidl K, Rameken M, Drogemuller A, et al. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *J Am Coll Cardiol* 2002;39:1436-42.
8. Black IW, Fatkin D, Sagar KB, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation. A multicenter study. *Circulation* 1994;89:2509-13.
9. Saeed M, Rahman A, Afzal A, et al. Role of transesophageal echocardiography guided cardioversion in patients with atrial fibrillation, previous left atrial thrombus and effective anticoagulation. *Int J Cardiol* 2006;113:401-5.

10. Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. *J Am Coll Cardiol* 2001;37:691-704.
11. Manning WJ, Weintraub RM, Waksmonski CA, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995;123:817-22.
12. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-429.
13. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;344:1411-20.
14. Akdeniz B, Türker S, Öztürk V, et al. Cardioversion under the guidance of transesophageal echocardiography in persistent atrial fibrillation: results with low molecular weight heparin. *Int J Cardiol* 2005;98:49-55.
15. Collins LJ, Silverman DI, Douglas PS, et al. Cardioversion of nonrheumatic atrial fibrillation. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. *Circulation* 1995;92:160-3.
16. Jaber WA, Prior DL, Thamilarasan M, et al. Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: a transesophageal echocardiographic study. *Am Heart J* 2000;140:150-6.
17. Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes following cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol* 2013;61:1998-2006.
18. Flaker G, Lopes RD, Al Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol* 2014;63:1082-7.
19. Husted S, De Caterina R, Andreotti F, et al. Non-vitamin K antagonist oral anticoagulants (NOACs): no longer new or novel. *Thromb Haemost* 2014;111:781-2.
20. De Caterina R, Husted S, Wallentin L, et al. General mechanisms of coagulation and targets of anticoagulants (section I). Position paper of the ESC Working Group on Thrombosis–Task Force on Anticoagulants in Heart Disease. *Thromb Haemost* 2013;109:569-79.
21. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;33:2719-47.
22. Vidal A, Vanerio G. Dabigatran and left atrial appendage thrombus. *J Thromb Thrombolysis* 2012;34:545-7.
23. Di Biase L, Burkhardt JD, Gilbert G, et al. Dabigatran has a higher risk of left atrial appendage thrombus formation in patients with AF when compared to warfarin and rivaroxaban. *Circulation* 2013. [Dallas, USA, Abstract 14308].
24. Hammerstingl C, Pötzsch B, Nickenig G. Resolution of giant left atrial appendage thrombus with rivaroxaban. *Thromb Haemost* 2013;109:583-4.
25. Takasugi J, Yamagami H, Okata T, et al. Dissolution of the left atrial appendage thrombus with rivaroxaban therapy. *Cerebrovasc Dis* 2013;36:322-3.
26. Kawakami T, Kobayakawa H, Ohno H, et al. Resolution of left atrial appendage thrombus with apixaban. *Thromb J* 2013;11:26.
27. Dobashi S, Fujino T, Ikeda T. Use of apixaban for an elderly patient with left atrial thrombus. *BMJ Case Rep* 2014;2014.
28. Lambers M, Nickenig G, Hertfelder HJ, et al. Direct acting oral anticoagulants are more effective than vitamin-K-antagonists for the resolution of established left atrial thrombi in patients with atrial fibrillation. *Clin Res Cardiol* 2014. [Abstract v1324].
29. Perzborn E, Roehrig S, Straub A, et al. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol* 2010;30:376-81.
30. Conway DS, Buggins P, Hughes E, et al. Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. *J Am Coll Cardiol* 2004;43:2075-82.
31. Lim HS, Willoughby SR, Schultz C, et al. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol* 2013;61:852-60.
32. Kumagai K, Fukunami M, Ohmori M, et al. Increased intracardiovascular clotting in patients with chronic atrial fibrillation. *J Am Coll Cardiol* 1990;16:377-80.
33. Roldan V, Marin F, Blann AD, et al. Interleukin-6, endothelial activation and thrombogenesis in chronic atrial fibrillation. *Eur Heart J* 2003;24:1373-80.
34. Lip GY, Watson RD, Singh SP. ABC of atrial fibrillation. Drugs for atrial fibrillation. *BMJ* 1995;311:1631-4.
35. Vene N, Mavri A, Kosmelj K, et al. High D-dimer levels predict cardiovascular events in patients with chronic atrial fibrillation during oral anticoagulant therapy. *Thromb Haemost* 2003;90:1163-72.
36. Maehama T, Okura H, Imai K, et al. Systemic inflammation and left atrial thrombus in patients with non-rheumatic atrial fibrillation. *J Cardiol* 2010;56:118-24.
37. Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767-72.
38. Ridker PM. Role of inflammatory biomarkers in prediction of coronary heart disease. *Lancet* 2001;358:946-8.
39. Roldan V, Marin F, Marco P, et al. Hypofibrinolysis in atrial fibrillation. *Am Heart J* 1998;136:956-60.
40. Cai H, Li Z, Goette A, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. *Circulation* 2002;106:2854-8.
41. Roldan V, Marin F, Marco P, et al. Anticoagulant therapy modifies fibrinolytic dysfunction in chronic atrial fibrillation. *Haemostasis* 2000;30:219-24.
42. Luo GP, Ni B, Yang X, et al. von Willebrand factor: more than a regulator of hemostasis and thrombosis. *Acta Haematol* 2012;128:158-69.
43. Roldan V, Marin F, Muina B, et al. Plasma von Willebrand factor levels are an independent risk factor for adverse events including mortality and major bleeding in anticoagulated atrial fibrillation patients. *J Am Coll Cardiol* 2011;57:2496-504.
44. Ammash N, Konik EA, McBane RD, et al. Left atrial blood stasis and von Willebrand factor-ADAMTS13 homeostasis in atrial fibrillation. *Arterioscler Thromb Vasc Biol* 2011;31:2760-6.
45. Lip GYH, Lane D, van Walraven C, et al. Additive role of plasma von Willebrand factor levels to clinical factors for risk stratification of patients with atrial fibrillation. *Stroke* 2006;37:2294-300.
46. Conway DS, Pearce LA, Chin BS, et al. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage and platelet activation in 994 patients with nonvalvular atrial fibrillation. *Circulation* 2003;107:3141-5.
47. Gallego P, Roldan V, Lip GY. Novel oral anticoagulants in cardiovascular disease. *J Cardiovasc Pharmacol Ther* 2014;19:34-44.

48. Kuruilla M, Gurk-Turner C. A review of warfarin dosing and monitoring. *Proc (Bayl Univ Med Cent)* 2001;14:305-6.
49. Ogawa S, Koretsune Y, Yasaka M, et al. Antithrombotic therapy in atrial fibrillation: evaluation and positioning of new oral anticoagulant agents. *Circ J* 2011;75:1539-47.
50. Ansell J. Factor Xa or thrombin: is factor Xa a better target? *J Thromb Haemost* 2007;5:60-4.
51. Fareed J, Hoppensteadt D, Cunanan J, et al. Effect of dabigatran and rivaroxaban on thrombomodulin mediated activation of protein C and thrombin activated fibrinolysis inhibitor (TAFI). *FASEB J* 2012. [Abstract 832.7].
52. Monroe DM, Hoffman M. What does it take to make the perfect clot? *Arterioscler Thromb Vasc Biol* 2006;26:41-8.
53. Akdeniz B, Türker S, Öztürk V, et al. Cardioversion under the guidance of transesophageal echocardiography in persistent atrial fibrillation: results with low molecular weight heparin. *Int J Cardiol* 2005;98:49-55.
54. Fukuda S, Watanabe H, Shimada K, et al. Left atrial thrombus and prognosis after anticoagulation therapy in patients with atrial fibrillation. *J Cardiol* 2011;58:266-77.
55. Wrisley D, Giambartolomei A, Lee I, et al. Left atrial ball thrombus: review of clinical and echocardiographic manifestations with suggestions for management. *Am Heart J* 1991;121:1784-90.
56. Fraser AG, Angelini GD, Ikram S, et al. Left atrial ball thrombus: echocardiographic features and clinical implications. *Eur Heart J* 1988;9:672-7.

Appendix

Supplementary Table I. Published studies on LA/LAA thrombus on echocardiography and resolution with anticoagulation

Study	Anticoagulant	Findings
Akdeniz et al ⁵³ (observational)	Warfarin (target INR 2.0-3.0)	<ul style="list-style-type: none"> Thrombus was observed in 32 (15.4%) of 208 patients after 4-6 wk of warfarin therapy Of the 11 patients who underwent a control TEE, 7 (63.6%) exhibited thrombus resolution
Collins et al ¹⁵ (observational)	Warfarin (target INR 2.0-2.8)	<ul style="list-style-type: none"> Thrombus resolution in 86% of patients with AF after 4 wk of warfarin therapy
Seidl et al ¹⁷ (single-center observational)	Warfarin (target INR 2.0-3.0)	<ul style="list-style-type: none"> Thrombus was observed in the left atrium of 55 (7.7%) of the 719 patients in the TEE-guided group All 55 patients had their INR increased to 3-3.5 for 4 wk, and resolution of the LA thrombus was detected on TEE in 55% of patients Low resolution rate explained partially by the inclusion of patients with valvular AF (nearly one-third of study population)
Corrado et al ⁴ (observational)	Warfarin (target INR ≥ 2)	<ul style="list-style-type: none"> Resolution of atrial thrombi after 4 wk of warfarin therapy in 9 (81.8%) of 11 patients (95% CI 48.2-97.7%)
Jaber et al ¹⁶ (observational)	Warfarin (mean INR 2.2) or heparin	<ul style="list-style-type: none"> 174 patients with thrombi in LAC and LAA. 161 patients received anticoagulant therapy for 47 ± 18 d 80% success in resolving LAC and LAA thrombi as demonstrated by follow-up TEE. Better success in resolving LAA thrombi (82.5%) vs LAC thrombi (53.3%)
Fukuda et al ⁵⁴ (observational)	Warfarin (target INR ≥ 2)	<ul style="list-style-type: none"> 148 patients on warfarin therapy for >3 wk with subtherapeutic anticoagulation (INR 1.9 ± 0.7) LA thrombus was observed on TEE in 13 (8.8%) patients with nonvalvular AF LA thrombus was observed in 3 (3.6%) of 83 patients with sufficient anticoagulation (>3 wk)
Nagarakanti et al ⁵ (RE-LY, post hoc analysis)	Dabigatran 110 mg bid (D110); dabigatran 150 mg bid (D150); warfarin	<ul style="list-style-type: none"> 165 patients on D110 therapy, 162 patients on D150 therapy, and 88 patients on warfarin therapy were assessed using TEE 1.8% of D110 patients, 1.2% of D150 patients, and 1.1% of warfarin patients were positive for LA thrombi Thrombus resolution not reported
Vidal et al ²² (case study)	Dabigatran 150 mg bid	<ul style="list-style-type: none"> 59-year-old White woman had LAA thrombus detected by TEE Unable to achieve therapeutic INR with warfarin therapy so switched to dabigatran Resolution of thrombus achieved after 7 wk of dabigatran treatment
Hammerstingl et al ²⁴ (case study)	Rivaroxaban 15 mg od	<ul style="list-style-type: none"> 64-year-old man with LAA thrombus detected by TEE 4 wk of treatment with rivaroxaban was associated with decrease in thrombus size Complete thrombus resolution was identified after 6 wk of therapy
Takasugi et al ²⁵ (case study)	Rivaroxaban 10 mg od	<ul style="list-style-type: none"> 3 patients (2 males, 1 female) had presence of LAA thrombi detected by TEE Treatment with rivaroxaban led to resolution of thrombus within 8-33 d 2 patients had resolution after 8 d of therapy, with the other patient showing a reduction in thrombus size after 21 d and resolution after 33 d of therapy
Kawakami et al ²⁶ (case study)	Apixaban 5 mg bid	<ul style="list-style-type: none"> 72-year-old man with LAA thrombus identified by TEE 16 d of apixaban treatment led to complete thrombus resolution
Dobashi et al ²⁷ (case study)	Apixaban 2.5 mg bid	<ul style="list-style-type: none"> 86-year-old man with LA thrombus detected through TEE 11 wk of apixaban treatment resulted in almost complete thrombus resolution

Abbreviations: *bid*, twice daily; *od*, once daily; *LAC*, left atrial cavity.

Supplementary Table II. Inclusion/exclusion criteria for X-TRA study

Inclusion criteria:

- Men or women aged ≥ 18 y
- Hemodynamically stable nonvalvular AF or atrial flutter
- LA/LAA thrombus documented at baseline by TEE up to 72 h before the start of study drug treatment
- VKA/NOAC naive or untreated within 1 m before signing the informed consent form (treatment of up to 72 h with VKA, heparin, or a low molecular weight heparin is allowed before the start of study drug treatment)
- or
- VKA pretreated but under ineffective INR levels (<2.0 documented with ≥ 2 consecutive measurements ≥ 24 h apart) within last 6 wk
- Written informed consent
- Women of childbearing potential and men must agree to use adequate contraception when sexually active. This applies from signing of informed consent form until 30 d after the last study drug administration

Exclusion criteria:

- TIA within 3 d before study inclusion
- Severe, disabling stroke (modified Rankin score of 4-5, inclusive) within 3 m or any stroke within 14 d before start of study drug
- Acute thromboembolic events or thrombosis (venous/arterial) within the last 14 d before study inclusion
- Acute MI within the last 14 d before study inclusion
- Cardiac-related criteria
 - Previous intracardiac thrombus
 - Free-floating ball thrombus^{55,56}
 - Intracardiac tumor, eg, known presence of atrial myxoma
 - Known left ventricular or aortic thrombus
 - Active endocarditis¹⁵
- Active bleeding or high risk of bleeding contraindicating anticoagulant therapy
- Concomitant drugs/therapies
 - Indication for anticoagulant therapy for a condition other than nonvalvular AF or atrial flutter, eg, VTE
 - Concomitant use of anticoagulant drugs, including VKA or factor IIa or factor Xa inhibitors
 - Chronic ASA therapy >100 mg daily or dual antiplatelet therapy
 - Concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein, ie, all HIV protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, and posaconazole—if used systemically
- Concomitant conditions
 - Childbearing potential without proper contraceptive measures, pregnancy, or breastfeeding
 - Hypersensitivity to investigational treatment
 - Calculated CrCl <15 mL/min^a at the screening visit
 - Coagulopathy-associated hepatic disease leading to clinically relevant bleeding risk; any severe condition that would limit life expectancy to <3 m such as advanced malignancy
 - Planned invasive procedure with potential for uncontrolled bleeding or increased risk of stroke, including major surgery, cardiac catheterization, or CV before the end-of-treatment TEE
 - Inability to take oral medication
 - Ongoing drug addiction or alcohol abuse
- Any other contraindication listed in accordance with local marketing regulations for the experimental treatment
- Participation in a study with an investigational drug or medical device within 30 d before start of study medication
- Previous assignment to treatment during this study
- Inability to cooperate with the study procedures

Abbreviations: ASA, Acetylsalicylic acid; CrCl, creatinine clearance; CYP, cytochrome P450; HIV, human immunodeficiency virus; MI, myocardial infarction; TIA, transient ischemic attack; VTE, venous thromboembolism.

^a Creatinine clearance calculated according to the Cockcroft-Gault formula.